## REMARKS

Claims 1-23 were pending in this application. According to the December 20, 2001 Office Action, claims 1-23 were rejected. Applicant has amended claim 16, 18 and 19. Accordingly, claims 1-23 are under consideration. Applicant maintains that the amendments do not introduce any new matter.

**Rejection under 35 U.S.C. §112**

The Examiner rejected claims 16, 18 and 19 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In response, Applicant has amended claims 16, 18 and 19 to replace the term "Tween 80" with the corresponding chemical name --polyoxyethylene(20) sorbitan monooleate--. Applicant encloses herewith a copy of a page in Aldrich chemical catalog where "TWEEN 80"is identified by its chemical name.

**Rejection under 35 U.S.C. §103**

The Examiner rejected claims 1-4, 6-14 and 16-23 under 35 U.S.C. §103(a) as allegedly unpatentable over Mardente et al. in view of Cho et al. The Examiner also rejected claims 5 and 15 under 35 U.S.C. §103(a) as allegedly unpatentable over Mardente et al. in view of Cho et al. as applied to claims 1-4, 6-14 and 16-23 and further in view of Dua et al.

In response, Applicant respectfully traverses the Examiner's rejection. Mardente discloses pharmaceutical compositions for intranasal administration containing in a spray dosing feeder calcitonin dissolved in a substantially physiological solution of sodium chloride adjusted to a pH between 3.5 and 4.5 with citrate buffer and hydrochloric acid without any preservative. Cho teaches pharmaceutical formulations comprising a biologically active material such as calcitonin containing emulsification aids such as polysorbate 80. Dua discloses the influence of tonicity and viscosity on the intranasal absorption of salmon calcitonin in rabbits.

In contrast, the present invention relates to a liquid pharmaceutical composition comprising calcitonin or an acid addition salt thereof and citric acid and/or salt thereof in a

concentration from **about 10 to about 50 mM**, said composition being in a form suitable for nasal administration. Applicant would like to point out to the Examiner that the concentration of about 10 to about 50 mM of citric acid in the pharmaceutical composition of the present invention is a critical one. Not only is citric acid important in improving the bioavailability of nasally administered calcitonin (see Tables 1 on page 14 of the specification), the particularly claimed range of citric acid is critical on the stability of the claimed pharmaceutical composition. As indicated in Table 3 (see specification on page 16), citric acid concentrations between 10 and 50 mM were essential in improving the stability of a liquid calcitonin pharmaceutical composition since citric acid concentrations outside the claimed range (either higher or lower than the claimed range) were relatively unstable. Thus, if the citrate concentration is too low or too high, the stability of calcitonin decreases.

Mardente does not disclose citric acid concentrations in the claimed range. In fact, Mardente discloses citric acid amounts between 0.4 g per liter and 0.7 g per liter and for sodium citrate to between 0.4 g per liter and 0.7 g per liter. Thus, the maximum molar concentration for citric acid and/or its salt disclosed by Mardente is about 6.1 mM outside the claimed range. There is nothing in Mardente or in Cho or Dua alone or in combination that discloses or suggest the use of 10 to 50 mM citric acid or salt thereof to stabilize a liquid nasal calcitonin formulation. Accordingly, the Examiner is kindly requested to withdraw this rejection.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on March 20, 2002:

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Respectfully submitted,

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